# Recombinant latent transforming growth factor beta 1 has a longer plasma half-life in rats than active transforming growth factor beta 1, and a different tissue distribution.

**Wakefield LM, Winokur TS, Hollands RS, Christopherson K, Levinson AD, Sporn MB**

Laboratory of Chemoprevention, National Cancer Institute, Bethesda, Maryland 20892.

Transforming growth factor beta 1 (TGF-beta 1) is a key regulator of cell growth and differentiation. Under normal physiological conditions, it is made as a biologically latent complex whose significance is unknown. Previous work has indicated that active TGF-beta 1 has a very short plasma half-life in rats (Coffey, R. J., L. J. Kost, R. M. Lyons, H. L. Moses, and N. F. La-Russo. 1987. J. Clin. Invest. 80:750-757). We have investigated the possibility that latent complex formation may extend the plasma half-life of TGF-beta 1 and alter its organ distribution. Radiolabeled latent TGF-beta 1 was formed by noncovalent association of 125I-TGF-beta 1 with the TGF-beta 1 precursor "pro" region from recombinant sources. TGF-beta 1 in this latent complex had a greatly extended plasma half-life (greater than 100 min) in rats compared with active TGF-beta 1 (2-3 min). Whereas active TGF-beta 1 was rapidly taken up by the liver, kidneys, lungs, and spleen and degraded, TGF-beta 1 in the latent complex was largely confined to the circulation, and was less than 5% degraded after 90 min. The pharmacokinetics of TGF-beta 1 in the latent complex were shown to be critically dependent on the degree of sialylation of the complex. The results suggest that formation of latent complexes may switch endogenous TGF-beta 1 from an autocrine/paracrine mode of action to a more endocrine mode involving target organs distant from the site of synthesis.

PMID: 2254455, UI: 91072674

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# Immunogenetic studies of spontaneous abortion in mice. III. Non-H-2 antigens and gestation.

**Bobe P, Kiger N**

INSERM U 28, Hopital Broussais, Paris, France.

CBA/J (H-2k) females, mated with DBA/2 J (H-2d) or DBA/1 J (H-2q) males, exhibit a high rate of fetal resorption. In contrast, when H-2 identical CBA substrains (i.e. CBA/Ca and CBA/N) are used, this phenomenon is not observed. On the other hand, before mating with DBA/2 J males, pre-immunization of CBA/J females with spleen cells coming from BALB/c J or (DBA/2 x BALB/c J) F1 males (and not from other H-2d identical males whatever their Mls alleles) has significantly decreased the fetal resorption rate. Thus, immunization against determinants other than classical H-2d (K, I, D, L) antigens (transmitted as a dominant character and different from Mls determinants) can elicit anti-abortive effects. Furthermore, it was observed that the spleen cell endowed with the anti-abortive effects was neither a T nor a B lymphocyte. In contrast, peritoneal cells were able to reproduce the phenomenon, indicating that it may be mediated by a cell of the macrophage-monocyte lineage. Finally, a first gestation was substituted for allo-immunization of CBA/J females. The anti-abortive effects of a first pregnancy by BALB/c J males (and not by other H-2k syngeneic or H-2d allogeneic males) was observed in the course of a second pregnancy sired by DBA/2 J males. These data can be interpreted in terms of maternal recognition of an antigen present on both macrophages and trophoblast cells and necessary for a successful gestation, which is coded for by genes outside the K, I, D, L regions.

PMID: 2614072, UI: 90131802

1: *J Immunol* 1985 Mar;134(3):1594-8 Related Articles, Books, LinkOut

# Immunologic consequences of vaccination against abortion in mice.

**Chaouat G, Kolb JP, Kiger N, Stanislawski M, Wegmann TG**

CBA/J female mice have a high rate of fetal resorption when mated with DBA/2J males. This fetal wastage can be dramatically reduced by immunizing the female with BALB/cJ but not DBA/2J spleen cells. We report here that immunization with BALB/cJ (but not DBA/2J) spleen cells leads to 1) anti-paternal MHC antibody that is predominantly of the IgG1 isotype, and which disappears from the serum during pregnancy; 2) increased active suppression in both the spleen and placenta; and 3) an ability to adoptively transfer the fetal protection and placental suppression with serum from the immunized mice. Congenic absorption studies before adoptive transfer indicate that the active component of the serum is also directed against the paternal MHC haplotype. These results indicate that maternal humoral immunity can lead to increased fetal protection in correlation with local active suppression in the placenta. They also suggest an expansion of the placental immunoabsorbent hypothesis to include the induction of active suppression against maternal cell-mediated immunity.

PMID: 3968429, UI: 85106238

1: *Am J Reprod Immunol Microbiol* 1988 Apr;16(4):146-50



# Vaccination against spontaneous abortion in mice by preimmunization with an anti-idiotypic antibody.

**Chaouat G, Lankar D**

U 262 INSERM, Maternite Baudelocque, Paris, France.

CBA/J females mated with DBA/2 display a high level of fetal wastage which can be corrected by anti-Balb/c vaccination. A batch of CBA/J anti-(CBA/J anti-Balb/c) antiserum was raised. This serum was characterized as anti-idiotypic by various techniques, including a solid-phase radioimmunoassay. Such a serum proved to confer protection against resorptions when injected into CBA/J mice mated with DBA/2. However, the kinetics of the effect pointed to the need for administration in early pregnancy for successful protection. The significance of these data, and the possible mechanism(s) by which the serum acts, are discussed.

PMID: 3421406, UI: 88338869

1: *J Assist Reprod Genet* 1996 Sep;13(8):669-74 Related Articles, Books



# The effect of activin-A on the development of mouse preimplantation embryos in vitro.

**Orimo T, Taga M, Matsui H, Minaguchi H**

Department of Obstetrics and Gynecology, Yokohama City University School of Medicine, Japan.

PURPOSE: Our purpose was to clarify the involvement of transforming growth factor-beta (TGF-beta) family in the regulation of preimplantation embryo development. METHODS: The effects of activin-A and TGF-beta on the rates of morula and blastocyst formations as well as on the cleavage velocity of a mouse two-cell embryo in vitro were analyzed. The gene expressions of these two growth factors in various developmental stages were also studied using RT-PCR. RESULTS: Activin-A at a concentration of 0.2 ng/ml significantly stimulated not only the rate of morula formation but also the velocity of embryo cleavage, whereas no significant effect was found with TGF-beta. RT-PCR revealed that activin-A subunit mRNA, but not TGF-beta mRNA, was detected in preimplantation mouse embryo at any developmental stage. CONCLUSIONS: Activin-A plays an important role in the regulation of preimplantation mouse embryo development in an autocrine fashion.

PMID: 8897128, UI: 97052494

# Granulocyte-macrophage colony stimulating factor (GM-CSF): one of a family of epithelial cell-derived cytokines in the preimplantation uterus.

**Robertson SA, Seamark RF**

Department of Obstetrics and Gynaecology, University of Adelaide, Australia.

Granulocyte-macrophage colony stimulating factor (GM-CSF) is one of a number of lympho-haemapoietic cytokines, including CSF-1, interleukin-6 (IL-6) and leukaemia inhibitory factor (LIF) now known to be synthesized by epithelial cells in the murine uterus. GM-CSF synthesis is regulated primarily by the ovarian steroid hormone oestrogen, but is also subject to modulation by factors including a seminal component of seminal vesicle origin which stimulates a 20-fold increase in luminal fluid content at mating, and bacterial lipopolysaccharide (LPS) and the T-lymphocyte and natural killer (NK) cell product interferon-gamma (IFN gamma). In the non-pregnant mouse GM-CSF synthesis peaks at oestrus. Synthesis is maintained at comparable or moderately higher levels during the preimplantation period of pregnancy and in the non-decidualized endometrium during mid gestation. An embryotrophic activity is suggested by studies in vitro that indicate that GM-CSF stimulates attachment and outgrowth of blastocysts. It is postulated that GM-CSF is of major importance to the physiology of pregnancy through its role as a component of a local cytokine circuit acting to recruit and regulate function of endometrial leukocytes, and by its action as interlocutor and important effector arm in embryo-maternal interactions during gestation.

Publication Types:
- Review
- Review, tutorial

PMID: 1461994, UI: 93096933

1: *Mol Cell Endocrinol* 2000 May 25;163(1-2):81-7 Related Articles, Books, LinkOut



# The roles of activins, inhibins and estrogen in early committed follicles.



**Findlay JK, Drummond AE, Britt KL, Dyson M, Wreford NG, Robertson DM, Groome NP, Jones ME, Simpson ER**

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[Medline record in process]

The hypothesis that activin and inhibin are autocrine/paracrine mediators of ovarian folliculogenesis has a solid basis. In mouse and rat models, granulosa cells (GC) of committed follicles express mRNA and protein for the activin/inhibin subunits and mRNA for the activin receptors (type I and II). Dimeric inhibin-A and -B are produced by postnatal ovarian cell dispersates and (GC) in culture. Similar levels of inhibin-A and -B are produced by postnatal ovarian cells, but thereafter as the ovary develops, inhibin-A becomes the predominant form. Activin was more effective than transforming growth factor-beta (TGF-beta) in enhancing follicle stimulating hormone (FSH)-stimulated inhibin production by ovarian cells. Evidence for a local regulatory role of estrogen in the ovary is also accumulating. Murine models of estrogen receptor (ERalpha or ERbeta) disruption produce mice with abnormal ovarian phenotypes. Female mice, which lack the capacity to produce estrogen (ArKO mice), have arrested folliculogenesis, no corpora lutea, elevated levels of luteinising hormone (LH), FSH and testosterone and are infertile. These data are consistent with autocrine/paracrine actions of activin in the early growth of committed follicles and estrogen in follicular maturation.

PMID: 10963878, UI: 20419868

1: *Hum Reprod* 1991 Feb;6(2):294-8 Related Articles, Books, LinkOut



# A prospective study of the incidence, time of appearance and significance of anti-paternal lymphocytotoxic antibodies in human pregnancy.

**Regan L, Braude PR, Hill DP**

Department of Obstetrics and Gynaecology, University of Cambridge, UK.

The incidence and natural history of serum anti-paternal cytotoxic antibody (APCA) in normal pregnancy and spontaneous abortion was investigated prospectively in 306 women (64 primigravidae and 242 multigravidae), in order to establish whether serum APCA is a useful screening test in the diagnosis, treatment and prognosis for patients with recurrent pregnancy loss. Pre-pregnancy, serial pregnancy and post delivery serum samples were tested against partner's lymphocytes, using a microdroplet lymphocytotoxicity assay. The incidence of serum APCA in the 256 pregnancies successfully completed was 32%, compared with 10% amongst the 50 pregnancies ending in spontaneous abortion. The lower incidence of positive APCA tests in unsuccessful pregnancies was explained by our finding that positive APCA tests are related to the gestational age of the pregnancy and are rarely demonstrable before 28 weeks gestation. Since APCA usually disappears between pregnancies, its usefulness as a diagnostic test for immunotherapy against recurrent abortion should be questioned.

PMID: 2056027, UI: 91277157

# Maternal response to paternal trophoblast antigens.

**Mowbray J, Jalali R, Chaouat G, Clark DA, Underwood J, Allen WR, Mathias S**

Imperial College School of Medicine at St. Mary's, London, United Kingdom.

PROBLEM: What is the function of the immunoglobulin (Ig) G antibody bound to trophoblast in normal pregnancy, and what is the antigen? METHOD: IgG was acid eluted from term human placental microvesicles and reacted with the antigen, R80K, left on the vesicles. The eluted antibody was used to detect the antigen on monocytes, lymphocytes, and lymphoblastoid cell lines. The eluted antibody is highly polymorphic, but monoclonal antibodies (mAbs) were made against conserved regions of the molecule. These also reacted with the murine equivalent of the human R80K and were used in inhibition studies of natural killer (NK) cell killing and the mouse abortion models, CBA x DBA2 F1 resorption in CBA females, the endotoxin-induced resorption model, and a sonic stress-induced murine resorption model. RESULTS: All 600 syncytiotrophoblast microvesicle preparations of human term placenta had IgG antibody bound, elutable at pH 3.0. The eluted antibody reacted with about 15% of unrelated human placentae. In horses mares make detectable antibody early in pregnancy, at about the time of implantation. The IgG antibody was bound to an 80-kDa protein (R80K) also detected on B lymphocytes and monocytes. In HLA homozygous lymphoblastoid B cell lines, which reacted with one or more eluted antibodies, had a pattern of cytotoxicity independent of HLA Class I; and as a single 80-kDa peptide chain, R80K did not resemble HLA molecules. Genetic studies in horses show that of the two paternal allotypes of R80K detectable by placental alloantibodies, only one, usually the grandpaternal one, is present in all the placentae of a sibship. Two of 26 eluted human antibodies had affinity for K562 and inhibited killing by human peripheral blood NK cells. One mAb, BA11, against a conserved site on R80K inhibited killing of K562, and also reacted with the murine R80K homologue. BA11 inhibited murine NK cell killing and virtually completely inhibited three NK cell-dependent mouse resorption models. CONCLUSION: R80K protein is a target molecule for NK cell activity expressed on all placentae. It has a polymorphic alloantigenic determinant completely covered with maternal antibody in all successful term pregnancies. In murine NK cell-dependent models of abortion, a mAb against a monomorphic determinant present in human and murine

# Expression of inhibin/activin subunits and their receptors and binding proteins in human preimplantation embryos.

**He ZY, Liu HC, Mele CA, Barmat L, Veeck LL, Davis O, Rosenwaks Z**

Center for Reproductive Medicine and Infertility, New York Hospital-Cornell Medical Center, New York, USA.

PURPOSE: Our purpose was to study the role of inhibin/activin during embryogenesis. METHODS: Transcripts of inhibin/activin subunits (alpha, beta A, beta B), activin receptors (types I and II), and follistatin were detected by a reverse transcriptase-polymerase chain reaction in human reproductive cells and preembryos cultured alone or co-cultured with human endometrial cells. RESULTS: Transcripts of alpha, beta A, beta B subunits were all detected in granulosa luteal cells, but only beta A units were detected in endometrial stromal and decidualized cells. In human preimplantation embryos, none of these subunits were detected in embryos from the four-cell to the morula stage and only beta A subunits were detectable in blastocyst embryos. Activin receptors were detectable in all of the studied embryos and cells. Transcripts of beta A, activin receptors, and follistatin were differentially expressed in human preimplantation embryos cultured in vitro and their expressions were significantly enhanced with the presence of endometrial stromal cells. CONCLUSIONS: Our data suggest that there is a possible endometrium-embryo interaction via endometrial activins and preimplantation embryo receptors and that the embryonic expressions of these activins, their receptors, and binding proteins are dependent on embryonic stage.

Publication Types:
- Clinical trial
- Controlled clinical trial

PMID: 10079409, UI: 99179126

# Developmental expression of activin/inhibin beta A, beta B, and alpha subunits, and activin receptor-IIB genes in preimplantation mouse embryos.

**Lu RZ, Matsuyama S, Nishihara M, Takahashi M**

Department of Veterinary Physiology, University of Tokyo, Japan.

We demonstrated previously that activin A released the two-cell block of mouse embryos cultured in vitro and stimulated early embryonic development. We then confirmed immunohistochemically the presence of the beta A, beta B, and alpha subunits in early embryos together with the oviductal epithelium facing those embryos. The results of in situ hybridization and reverse-transcription polymerase chain reaction here show the presence of mRNA transcripts for activin/inhibin beta A, beta B subunits in the ovary, oviduct, unfertilized egg, and embryo at the early preimplantation stage. However, the mRNA of the inhibin alpha subunit was not expressed in any of these. Considering our previous demonstration of the immunoreactive beta A, and beta B subunits of activin/inhibin polypeptides in the cytoplasm of 1- and 2-cell embryos, we suggest that activins appearing in the oviduct and in embryos are not only transferred from the follicular fluids, but produced by the oviduct, oocytes, and embryos themselves. Since the mRNA of the inhibin alpha subunit was absent at those stages, the beta A and beta B subunits may not exist as the inhibin molecule. The mRNA of activin receptor-IIB was detected in the ovary, in embryos at the 1-cell and the 8-cell/morula stages, and also in the unfertilized egg, although to a lesser extent, but not in the oviduct or in the 2-cell-stage embryo either in vivo or cultured in vitro. These results suggest that activin is physiologically involved in the process of early development of mouse embryos.

PMID: 8286599, UI: 94114766

1: *Proc Nutr Soc* 1999 Feb;58(1):69-73 Related Articles, Books



# The influence of the maternal uterine immune response on placentation in human subjects.

**King A, Loke YW**

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The immunological relationship between the mammalian fetus and its mother during pregnancy has been considered similar to that between a transplanted allograft and its recipient ever since Medawar (1953) first proposed the concept of the 'fetus as an allograft' in the early 1950s. Based on this analogy, it has been assumed that implantation of the fetal placenta in the uterus would be controlled similarly by a maternal immune response mediated by T-cells recognizing paternally-derived alloantigens expressed by the placenta. Surprisingly, recent evidence suggests that implantation might involve predominantly a novel allogeneic recognition system based on natural killer cells rather than T-cells (Loke & King, 1995). The cellular and molecular basis of this local immune interaction between the fetal placenta and maternal uterus is now the focus of intense research interest. Since aberrant implantation can cause a variety of clinical problems, including miscarriage, intrauterine growth retardation and pre-eclampsia, an understanding of the immunological mechanism by which this process is controlled could lead to the development of regimens to improve fetal growth and development.

Publication Types:
- Review
- Review, tutorial

PMID: 10343342, UI: 99274810

# Transforming growth factor-beta1-deficient mice: identification of isoform-specific activities in vivo.

**Letterio JJ, Roberts AB**

Laboratory of Chemoprevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.

A remarkable range of activities has been ascribed to the family of proteins known as transforming growth factor-beta (TGF-beta). Each plays an important role in development and homeostasis, influencing mesenchymal-epithelial interactions, regulating cellular differentiation, and maintaining control of cell proliferation. Although in vitro comparisons of activity demonstrate a high degree of functional similarity, recent studies of mice with a targeted deletion of the TGF-beta1 gene reveal that true isoform-specific activities do exist in vivo and that the three mammalian isoforms are not functionally redundant. This approach has defined a unique role for TGF-beta1 in the establishment and maintenance of normal immune function, shed new light on the relevance of endogenous TGF-beta1 to the normal wound healing process, and expanded the list of known mechanisms of TGF-beta1 activity to include endocrine functions. Thus, the TGF-beta1-deficient mouse allows the definition of isoform-specific activities, providing an invaluable window through which to view the principal functions of TGF-beta1 in vivo.

Publication Types:
- Review
- Review, tutorial

PMID: 8691059, UI: 96272212

1: *Endocrinology* 1989 Oct;125(4):1857-62 Related Articles, Books



# Effects of transforming growth factors and inhibin-related proteins on rat preovulatory graafian follicles in vitro.

**Tsafriri A, Vale W, Hsueh AJ**

Department of Reproductive Medicine, School of Medicine, University of California-San Diego, La Jolla 93093.



In view of recent reports on ovarian production and action of transforming growth factors (TGFs) and inhibin-related proteins (inhibin, activin, and follistatin), we have examined the effects of these hormones on the function of preovulatory follicles in vitro. Individual preovulatory follicles were obtained from PMSG-treated rats and incubated with these hormones in the absence or presence of LH. Oocyte maturation and progesterone production were monitored. Treatment with TGF alpha alone, but not with TGF beta or inhibin-related proteins, mimicked the action of LH on oocyte maturation by inducing the resumption of meiosis in follicle-enclosed oocytes (56.6% and 80.6% oocytes resumed meiosis in the presence of 0.5 and 1.0 microgram/ml TGF alpha, respectively). In follicle cultures treated with LH to induce oocyte maturation, cotreatment with inhibin and TGF beta (30-50 ng/ml), but not other related hormones, partially inhibited LH-induced meiosis in follicle-enclosed oocytes (from 82% mature ova in the presence of LH to 51% and 55% mature ova with TGF beta and inhibin, respectively). In contrast to follicle cultures, none of the hormones tested significantly affected the spontaneous maturation of rat oocytes explanted from their follicles and cultured within their cumulus mass for 4 h. Treatment with TGF alpha, but not with TGF beta, inhibin, activin, or follistatin, stimulated progesterone production. The present study demonstrated that TGF alpha, like LH, induces oocyte maturation and progesterone production in preovulatory rat follicles. Furthermore, inhibin and TGF beta suppressed LH-induced resumption of meiosis in follicle-enclosed oocytes. Because these growth factors and inhibin-related proteins are synthesized by follicle cells, they may play important roles in regulating follicular development and activity.

PMID: 2791970, UI: 90005121

1: *Biol Reprod* 1998 May;58(5):1217-25 Related Articles, Books



# Seminal transforming growth factor beta1 stimulates granulocyte-macrophage colony-stimulating factor production and inflammatory cell recruitment in the murine uterus.

**Tremellen KP, Seamark RF, Robertson SA**

Department of Obstetrics and Gynaecology, University of Adelaide, South Australia, Australia.

Mating in rodents evokes an inflammatory-like reaction within the uterine endometrium, characterized by extensive infiltration and activation of macrophages, dendritic cells, and granulocytes. This response is initiated when seminal vesicle gland-derived factors in the ejaculate stimulate uterine epithelial cells to release proinflammatory cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF). Experiments in which seminal vesicle secretions were fractionated by Sephacryl S-400 chromatography and assayed in vitro for GM-CSF-stimulating activity revealed that the seminal moiety coeluted with transforming growth factor beta1 (TGFbeta1) in the 150-440-kDa range and was neutralized by anti-TGFbeta1 antibodies. Comparable amounts of recombinant TGFbeta1 stimulated GM-CSF release in cultures of uterine epithelial cells from estrous mice and, when instilled into the uterine lumen, caused an increase in GM-CSF content and an infiltration of leukocytes into the endometrium similar to the postmating response. These results show that seminal vesicular fluid contains TGFbeta1 at levels sufficient to be the primary causative agent in the postmating inflammatory cascade through induction of GM-CSF synthesis by uterine epithelial cells. Seminal TGFbeta1 is thus implicated as a key factor in initiation of the remodeling events and immunological changes that occur in the uterus during the preimplantation period of pregnancy.

PMID: 9603256, UI: 98264395

1: *Am J Reprod Immunol* 1999 Aug;42(2):124-33 Related Articles, Books, LinkOut

# TGF beta 2 mRNA expression and pregnancy failure in mice.

**Gorivodsky M, Torchinsky A, Zemliak I, Savion S, Fein A, Toder V**

Department of Embryology and Teratology, Sackler School of Medicine, Tel Aviv University, Israel.

PROBLEM: We describe here a pattern of transforming growth factor (TGF) beta2 mRNA expression at the fetomaternal interface in mice with high rate of resorptions as well as its expression following maternal immunopotentiation. METHOD OF STUDY: TGF beta 2 mRNA expression was evaluated in the uteroplacental units of mice with spontaneous (CBA/J x DBA/2J mouse combination) or cyclophosphamide (CP)-induced pregnancy loss. The effect of immunopotentiation on TGF beta 2 mRNA expression was determined in CP-treated females who underwent nonspecific immunostimulation with xenogeneic (rat) leukocytes. A quantitative analysis of TGF beta 2 mRNA level was performed using RNase protection assay. Distribution of TGF beta 2 mRNA transcripts at the fetomaternal interface was studied by in situ hybridization analysis. RESULTS: RNase protection analysis revealed four TGF beta 2 specific mRNA forms (330, 270, 230, and 170 bp) in the uteroplacental units of mice with either normal or decreased reproductive performance. A significant decrease (about 50%) in the level of TGF beta 2 mRNA was registered in the uteroplacental unit of mice with pregnancy loss as compared to the control mice. TGF beta 2 transcripts were abundant in the uterine epithelium and stroma. A specific hybridization signal was detected also in metrial gland cells and it was found to be substantially lower in CP-treated as compared to intact mice. In the resorbing uteroplacental unit, the expression of TGF beta 2 mRNA was completely lost in the uterine epithelium, and the number of TGF beta 2 mRNA-positive metrial gland cells was lower as compared to the control. Immunopotentiation decreased the resorption rate in mice with CP-induced pregnancy loss and caused a dramatic increase in TGF beta 2 mRNA expression: the level of TGF beta 2 mRNA was found to be higher by 2.0-3.2 fold in the uteroplacental unit of immunized as compared to nonimmunized CP-treated mice. CONCLUSIONS: These data suggest that distortion of TGF beta 2 expression at the fetomaternal interface may be associated with pregnancy failure. It seems that beneficial effect of maternal immunostimulation may at least partly be due to the strong increase in TGF beta 2 mRNA expression at the fetomaternal interface.

1: *FASEB J* 1992 Mar;6(6):2344-8 Related Articles, Books, LinkOut

# HLA and maternal-fetal recognition.

**Hunt JS, Orr HT**

Department of Pathology and Oncology, University of Kansas Medical Center, Kansas City 66103.

Despite genetic differences, mothers do not reject their semiallogeneic embryos. Regulated expression of the major histocompatibility antigens (HLA) by placental trophoblast cells, which intervene between the embryo and maternal blood and tissues, is now believed to play an important role in this surprising feature of pregnancy. Transcription and translation of the highly polymorphic class I HLA-A, -B, -C genes whose products stimulate graft rejection are blocked in trophoblast cells. Instead, these cells express HLA-G, a nonpolymorphic gene. Moreover, the cells do not express class II HLA-D antigens, and factors such as interferons that usually enhance HLA expression have no effect on trophoblast cells in situ. Thus, multiple regulatory mechanisms prevent the cells that sequester the embryo from the mother from expressing the potentially deleterious paternal HLA antigens, immunological rejection is avoided and successful pregnancy ensues.

Publication Types:
- Review
- Review, tutorial

PMID: 1544544, UI: 92184070

# Mouse model for the treatment of immune pregnancy loss.

**Toder V, Strassburger D, Carp H, Irlin I**

Department of Embryology and Teratology, Tel-Aviv University Medical School, Israel.

Spontaneous abortions can be associated with preimplantation embryo loss, implantation problems and a variety of postimplantation pregnancy failures. The long list of possible causes for the postimplantation pregnancy loss includes, among others, genetic abnormalities in fetus, anatomical abnormalities of the uterus, endocrinological insufficiency, and microbiological problems. However, more than 50% of recurrent miscarriages still have no recognized causes. The concept that many such abortions may be immunologically mediated has gained increasing support over the years. Moreover, immunization of such women with husband's or third party leukocytes has resulted in more than 70% of subsequent pregnancies resulting in live births. Since neither the mechanisms leading to pregnancy loss nor the success of immunotherapy are clear, the set-up of animal models for recurrent abortions would be of supreme significance. Our recent data show that immunopotentiation of maternal immune system by Complete Freund Adjuvant significantly improves pregnancy rate in CBA x DBA/2 mouse combination with high percentage of fetal resorptions. This effect is followed by decrease of IL 2 production in spleen; increase of MAC 1-positive cells at placenta; amplification of suppressive activity of local and systemic lymphocytes and by reverse of embryotoxic effect of maternal serum. Data obtained in this model seems to be valuable in substantiation of rationale for nonspecific immunotherapy of human abortions.

Publication Types:
- Review
- Review, tutorial

PMID: 1741938, UI: 92075136

# Resorption of CBA/J x DBA/2 mouse conceptuses in CBA/J uteri correlates with failure of the feto-placental unit to suppress natural killer cell activity.

**Gendron RL, Farookhi R, Baines MG**

Department of Physiology, McGill University, Montreal, Quebec, Canada.

Lipid extraction was used to study the natural killer (NK) suppressive activity of individual feto-placental units. Normal pregnancies showed a lipophilic NK cell suppressive factor that was gestational day specific. Feto-placental units from CBA/J x DBA/2 pregnancies were deficient in the NK cell suppressive factor when compared to normal CBA/J x BALB/c pregnancies. The frequency of non-suppressive feto-placental units from CBA/J x DBA/2 pregnancies correlated with the frequency of feto-placental units infiltrated with NK cells and the frequency of spontaneous resorption. Our results implicate a deficiency of NK suppressive activity in the feto-placental unit as a contributing factor in spontaneous fetal resorption.

PMID: 2374121, UI: 90325168

1: *Reprod Fertil Dev* 1989;1(3):183-90, discussion 191



# Maternal immune response to pregnancy.

**Billington WD**

Department of Pathology, Medical School, University of Bristol, U.K.

The pregnant female is exposed to a variety of potentially immunogenic foreign antigens on her allogenic intra-uterine conceptus. The extent to which maternal antibodies and cell-mediated immune responses to these antigens are relevant to the paradoxical survival of the fetal allograft is not clearly established. The key to the maintenance of pregnancy lies in the trophoblast. This tissue prevents significant entry of maternal lymphocytes to the fetus and is most likely to protected from maternal immune rejection by features of its cell surface molecular structure and/or its synthesis of factors that render it insusceptible to antibody- or cell-mediated immune lysis in vivo. An alternative, or complementary, protective system, involving maternal recognition and immunoregulatory processes that deviate responses away from the expected rejection reactions, may also operate but has not yet been convincingly demonstrated. Such a mechanism is unlikely to involve the classically defined histocompatibility classically defined histocompatibility antigen system, at least in human pregnancy, where there is an absence of Class I antigens from the trophoblast but increasing evidence of trophoblast-associated antigens and related immune responses. It remains to be established whether unexplained recurrent miscarriage in women and spontaneous abortion in animal models is caused by failure of maternal immunoregulatory control or by non-immunological factors. This is relevant to the validity of immunotherapeutic approaches to the prevention of early fetal loss.

Publication Types:
- Review
- Review, tutorial

PMID: 2682805, UI: 90047819

1: Am J Reprod Immunol 1995 Feb;33(2):176-81 Related Articles, Books, LinkOut

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# Fertility among women with recurrent spontaneous abortions--the effect of paternal cell immunization treatment.

**Cowchock FS, Smith JB.**

Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

PROBLEM: The risk of women whose chief complaint is recurrent spontaneous abortions (RSA) for secondary infertility (infecundability) has not been evaluated prospectively. The effect of paternal mononuclear cell immunization on conception rates is unknown. METHOD: Two hundred women whose chief complaint was RSA were randomly assigned to be immunized with paternal mononuclear cells either before or after (up to 6 postmenstrual weeks) conception. Fertility rates (both conception and live birth) were evaluated for the group immunized before conception and compared to those for the control group, who were not immunized until after conception, using life table and multiple logistic regression analyses. RESULTS: Prospectively ascertained, age-related conception rates for nonimmunized RSA controls appeared to be similar to those for general populations. Immunization before pregnancy had no significant effect (power +/- 14%) on rates of conception (66% before, 77% after) or time to conceive (median weeks before 19.5, after 27.0). Live birth rates (before 59%, after 63%) were also similar for both groups (P = 0.7). CONCLUSION: Women whose only prior complaint was RSA were not at high risk for secondary infecundability, and immunization did not alter either conception rates or time to conceive. Postponement of immunization until after conception did not affect live birth rates for women selected for study because they did not have a history of prior infecundability or early repeated miscarriages.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 7646769 [PubMed - indexed for MEDLINE]